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A Preliminary Study of Low-Dose Angiotensin 1-7 Plus the Pineal Hormone Melatonin in the Treatment of Human Systemic Diseases other than Cancer and Autoimmune Pathologies

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Abstract

The recent advances of the psychoneuroimmunology have demonstrated the existence of a physiological anti-inflammatory antitumor neuroendocrine axis, mainly constituted by the pineal gland through its indole hormone melatonin (MLT) and the ACE2-angiotensin 1-7 (Ang 1-7) system. Moreover, most human systemic diseases, including cancer, autoimmunity, metabolic, cardiovascular, and neurodegenerative pathologies, have appeared to be characterized by an endogenous deficiency in the functionless of the pineal gland and ACE-ACE2 system. Therefore, the exogenous correction of MLT and Ang 1-7 deficiency could improve the clinical control of human systemic diseases. On these bases, a preliminary study of MLT plus Ang 1-7 was planned in patients suffering from systemic alterations other than cancer and autoimmunity. The study included 33 consecutive patients, whose pathologies were, as follows: cardiovascular pathologies: 9; pulmonary diseases: 7; metabolic syndrome: 7; neurodegenerative pathologies: 10. Both Ang 1-7 and MLT were given orally, at a dose of 0.5 mg/day in the morning for Ang 1-7, and at a dose of 10 mg/day in the evening for MLT. The treatment was well tolerated in all patients, and no-therapy related toxicity occurred. On the contrary, most patients experienced a relief of anxiety and asthenia, and an improvement in both mood and quality of sleep. Moreover, most patients referred an increased diuresis. Blood pressure values progressively became within the normal range in hypertensive patients. On the same way, glucose and cholesterol levels progressively decrease on therapy in diabetic and hypercholesterolemic patients, respectively. Patients with pulmonary disturbance referred an important enhancement in the expectoration, with a following improvement in the respiratory symptomatology. Finally, an apparent improvement in cognitive and motor functions was achieved in patients with neurodegenerative pathologies. These preliminary results would suggest a future medical possibility to treat the human systemicdiseases by simply correcting their endogenous neuroendocrine deficiencies, mainly those involving the functions of the pineal gland and ACE2-Ang1-7 system.

Keywords : *ACE2; Angiotensin 1-7; Cardiovascular pathologies; Human systemic diseases; Melatonin; Metabolic syndrome; Neurodegenerative diseases; Pineal gland.*

Introduction

The dramatic planetary eventof Covid 19 infection has demonstrated the fundamental role of ACE2 and its enzymatic product, the angiotensin 1-7 (Ang 1-7), in the regulation of the inflammatory response and coagulation processes, which before Covid 19 infection was known only to some research centres (1-5). In fact, it was known since more than 10 years that Ang 1-7

exerts a fundamental anti-inflammatory, anti-tumor and antithrombotic effects, as well as several protective biological functions on both heart and nervous system (1-5), by probably representing the main endogenous molecule provided by potential therapeutic effects on most human systemic diseases, and least to contribute to their resolution (1-6). ACE2 receptors are widely expressed, particularly at endothelial levels (1-5). Moreover, it has been also demonstrated the existence of a specific renin-ACE-ACE2 system at brain level (7), which would play a fundamental role in the control of neuroinflammatory processes (7-9), which are responsible for the neuronal death. Then, the neurodegenerative diseases would be due at least in part to an unbalance between ACE and ACE2 expression, with a prevalence of ACE expression with respect to that of ACE2, and a consequent enhanced production of angiotensin II (Ang II) instead of Ang 1-7, and the following induction of neuroinflammatory processes because of the inflammatory action of Ang II (1-5). Unfortunately,despite its potential therapeutic activity in the treatment of several systemic pathologies, already demonstrated in experimental conditions (1-6), mainly the hypotensive, cardioprotective, neuroprotective, antitumor, anti-inflammatory, anti-thrombotic and anti-fibrotic effects, very few clinical studies have been performed until now to confirm the wide therapeutic properties of Ang 1-7 also in human diseases. Moreover, most clinical studies have employed Ang 1-7 at high doses, ranging from 0.1 to 0.5 mg/kg body weight (10,11). However, according to the recent advances in the area of psycho-neuro-endocrino-immunology (PNEI) (12,13), ACE2-Ang 1-7 axis cannot be investigated in an separate manner, since it is a part of a systemic anti-inflammatory anti-tumor bioregulatory neuroendocrine system, which is essentially constituted of Ang 1-7 itself, the pineal gland through its most known hormone, the indole melatonin (MLT) (14), the endocannabinoid system (15), and the cardiac endocrine function in terms of the production of atrial natriuretic peptide (ANP), which is also provide d by anti-inflammatory antitumor effects (16). Therefore, the biological significance of Ang 1-7 needs to be analysed in relation to at least the pineal gland, the cannabinoid system, and the cardiac hormone ANP. In fact, it has been demonstrated that MLT may stimulate ACE2 expression, with a following enhanced endogenous production and activity of Ang 1-7 itself (17). In addition, it has been shown that cannabinoid agonists may stimulate MLT secretion from the pineal gland (18). MLT, cannabinoids, and Ang 1-7 display their anti-inflammatory, antitumor, and neuro-cardio-protective effects through several mechanisms, one of the most important would be represented by the inhibition of IL-17 secretion (19-21), which exerts inflammatory, pro-tumoral, and cardiovascular toxic effects (22,23), by representing one of the main toxic endogenous molecules. The metabolic syndrome would also be due to an enhanced inflammatory status induced at least in part by IL-17 itself by promoting the adipocyte secretion of other inflammatory cytokines, including IL-6 and TNF-alpha, which would allow the insulin resistance (24). Finally, preliminary clinical studies have suggested that the concomitant administration of MLT may enhance the biological activity of Ang 1-7 (25), with a clinical activity at a dose markedly lower with respect to that reported in the literature (10,11), and this event would be probably depending on the stimulatory action of MLT on ACE2-Ang 1-7-Mas receptor axis (17). On these bases, a preliminary clinical study with low-dose Ang 1-7 in association with MLT was performed in patients with systemic pathologies other than cancer and autoimmune diseases, whose treatment would require a more precise definition, to evaluate the tolerability of treatment, its subjective effects, and its potential therapeutic activity, even though in a very preliminary way.

Patients and Methods

The study included 33 consecutive patients suffering from systemic diseases other than cancer and autoimmune pathologies (M/F: 20-13; median age: 68 years, range 41-82). The dominant pathology consisted of cardiovascular disturbances in 9, pulmonary diseases in 7, metabolic syndrome in 7, and neurodegenerative disease in the remaining 10 subjects.After the approval by the Ethical Committee, the clinical protocol was explained to all patients and to their parents, and written consent was obtained. Ang 1-7 was given orally in gastro-protected capsules at a dose of 0.5 mg/day in the morning. MLT was given orally at 10 mg/day in the evening, generally 30 minutes prior to sleep, according to its physiological light/dark circadian secretion (15). Patients suffering from Parkinson's disease were concomitantly treated with L-Dopa, while no define therapy was followed by patients affected by other neurodegenerative

pathologies. Within the group of six hypertensive patients, four of them entered to study at the beginning of disease, while the other two were already under treatment with angiotensin-receptor blockers (ARB). Finally, within the group of patients affected by metabolic syndrome, only two were under therapy with oral antidiabetics. Patients were followed for 6 consecutive months, with clinical, instrumental, and laboratory controls and 2-month intervals.

Results

The clinical characteristics of patients and their subjective and objective response to therapy are reported in Table 1. No therapy-related toxicity was observed, and particularly no important hypotension occurred. On the contrary, most patients experienced an improvement in the quality of sleep and mood, a relief of anxiety, and a better sense of force, with a complete resolution of astheny in 7/11 (64%) patients with important astheny prior to study. Two patients only referred a paradoxical worsening of quality of sleep, which, however, was limited to the first weeks of therapy. Moreover, an evident increase in the diuresis was referred in 22/33(67%) patients, which was particularly evident in the two patients with left ventricular failure, one of them interrupted the diuretic therapy. Blood pressure declined in all hypertensive patients, and one of the two patients under therapy with ARB interrupted the treatment because of the control of blood pressure achieved under MLT and Ang1-7. Patients affected by chronic bronchitis and bronchiectasis experienced an enhanced expectoration and a consequent improvement in their respiratory capacity. Cholesterol and glucose levels progressively declined in patients with metabolic syndrome, even though with a different rapidity. Finally, an apparent improvement in the cognitive functions and in motor disturbances was observed in Alzheimer's disease and in Parkinson's disease, respectively, while no benefit was seen in patients with motoneuron disease.

Table 1. *Clinical characteristics of patients treated by Ang 1-7 plus MLT and their single clinical response*

CASES	SEX	AGE	PATHOLOGY	CLINICAL RESULTS
CARDIOVASCULAR DISEASES				
1	M	65	Arterial hypertension	Slow normalization of blood pressure
2	M	72	Arterial hypertension	Interruption of previous hypotensive therapies
3	M	58	Cardiomyopathy	Improvement of ejection fraction
4	F	52	Arterial hypertension	Slow decline in blood pressure
5	M	58	Arterial hypertension	Rapid blood pressure normalization
6	F	82	Arterial hypertension	Control of hypertensive peaks
7	M	71	Cardiac ischemia	Stabilization of disease
8	F	69	Arterial hypertension	Slow normalization of blood pressure
9	M	68	Cardiac ischemia	Stabilization of disease
PULMONARY DISEASES				
1	M	66	Left ventricular failure	Evident enhancement of diuresis
2	M	67	Chronic bronchitis	Improvement of dyspnoea
3	F	61	Bronchiectasis	Low increase in expectoration
4	M	65	Bronchiectasis	Evident enhancement of expectoration
5	M	62	Pulmonary heart	Improvement of dyspnoeaand astheny
6	M	82	Chronic bronchitis	Enhanced expectoration
7	M	70	Chronic bronchitis	Improvement of dyspnoea
METABOLIC SYNDROME				
1	M	73	Diabetes mellitus	Normalization of glycosylate haemoglobin
2	M	62	Diabetes mellitus	Normalization of glycemia
3	F	76	Diabetes mellitus	Low decline in glucose levels
4	M	61	Hypercholesterolemia	Normalization of cholesterol levels
5	F	52	Hypercholesterolemia	Low decline in cholesterol levels
6	F	81	Hepatic steatosis	Stabilization of steatosis
7	M	71	Hepatic steatosis	Improvement in ecography features

NEURODEGENERATIVE DISEASES				
1	F	78	Alzheimer's disease	Improvement of mood
2	M	41	Motoneuron disease	Progressive worsening
3	F	81	Alzheimer's disease	Stabilization of the cognitive functions
4	M	62	Parkinson's disease	Little improvement of motor coordination
5	M	68	Parkinson's disease	Trembling improvement
6	F	48	Motoneuron disease	Stabilization of disease
7	F	72	Parkinson's disease	Evident improvement of motor coordination
8	M	77	Alzheimer's disease	No apparent benefit
9	F	78	Alzheimer's disease	Progressive improvement of cognitive functions
10	F	75	Parkinson's disease	Reduced anxiety and relief of asthenia

Discussion

The results of this preliminary study would show that low-dose Ang 1-7 in association with the pineal hormone MLT may be a very well tolerated and effective neuroendocrine regimen in the treatment of the most common human diseases, including cardiovascular, metabolic, and neurodegenerative disturbances. Previous studies had already shown that both MLT alone (15,26) and Ang 1-7 alone (1-6) may exert potential therapeutic effects in the treatment of hypertension, cardiac ischemia, metabolic alterations, and neuroinflammatory diseases. Then, this preliminary clinical investigation would suggest that the combination of low-dose Ang 1-7 and MLT may allow more promising therapeutic results with respect to the single agents, because of their reciprocal stimulatory connections, by confirming that some of the main therapeutic molecules may be identified and researched within human body itself. Therefore, the neuroimmune regimen of MLT and Ang 1-7 could be proposed as an experimental therapy of human diseases, for whom no standard effective therapeutic protocol has been established, such as the neurodegenerative pathologies, while it could be integrated with the standard therapies in the case of diseases, for whom an effective therapy is already available, including metabolic syndrome and cardiovascular pathologies, to make more physiological their clinical management. The proposal of the concomitant administration of MLT plus Ang 1-7 in the treatment of human systemic pathologies is justified by the fact that they have been already appeared to be characterized by a diminished and altered endogenous secretion of both MLT and Ang 1-7 (27-30). Therefore, the future medical therapies of human systemic diseases could simply consist of the correction of their main related neuroendocrine anomalies, such as those of the pineal MLT and the ACE2-Ang 1-7 axis, whose bioregenerative properties have been well documented. Further clinical studies will be required to better establish dose and schedule of administration of the neuroimmune regimen with MLT and low-dose Ang 1-7.

References

[1] Simoes-e-Silva AC, Silveira KD, Ferreira AJ, Teixeira MM. ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. Br J Pharmacol 169:477-492, 2013.

[2] Rodrigues-Prestes TR, Pessoa-Rocha N, Miranda AS, Teixeira AL, Simoes-e-Silva AC. The anti-inflammatorypotential of ACE2/angiotensin-(1-7)/Mas receptor axis:evidence from basic and clinical research. Curr Drug Trargets 18: 1301-13123, 2017.

[3] Cheng H, Wang Y, Wang GQ. Organ-protective effect of angiotensin-converting enzyme 2 and its effects on the prognosis of COVID-19. J Med Virol 92: 726-30, 2020.

[4] Peirò C,Moncada S. Substituting angiotensin-(1-7) to prevent lung damage in SARS-CoV-2 infection? Circulation 141: 1665-1666, 2020.

[5] Verdecchia P, Cavallini C, Spanevello A, Angeli F. The pivotal link between ACE2 deficiency and SARS-Cov-2 infection. Eur J InternMed 76: 14-20, 2020.

[6] Lissoni P, Porro G, Rovelli F, Lissoni A, Orfanò S, Galbanin J, Messina G, Merlin D, Porta E, Di Fede G. A review on the potential therapeutic properties of angiotensin 1-7 in most systemic human diseases. Clin Res Hematol 3: 1-6, 2020.

[7] Xia H, Lazartigues E. Angiotensin-converting enzyme 2 in the brain: properties and future directions. J Neurochem 107: 1482-1494, 2008.

[8] Almeida-Santos An, Kangussu LM, Campagnole-Santos MJ. The renin-angiotensin system and the neurodegenerative diseases: a brief review.

[9] Pessoa-Rocha N, Simoes-e-Silva AC, Rodrigues-Prestes TR, Feracin V, Machado CA, Ferreira RN, Teixeira AL, Silva de Miranda. RAS in the central nervous system: potential role I neuropsychiatric disorders. Curr Med Chem 25: 3333-3352, 2018.

[10] Rodgers KE, Oliver J, di Zerega GS. Phase II/II dose escalation study of angiotensin 1-7 administered before and after chemotherapy in patients with newly diagnoses breast cancer. Cancer Chemother Pharmacol 57: 559-568, 2005.

[11] Forte BL, Slosky LM,ZhangH, Arnold MR, Staatz WC, Hay M, Largent-Milnes TM, Vanderah TW. Angiotensin-(1-7)/Mas receptor as an antinociceptive agent in cancer-induced bone pain. Pain 157: 2709-2721, 2016.

[12] Maestroni GJM. The immunoneuroendocrinerole of melatonin.J Pineal Res 14: 1-10, 1993.

[13] Ursin H. The psychology in psycho neuro endocrinology. Psychoneuro endocrinology 23: 555-570, 1998.

[14] Brzezinski A. Melatonin in humans. N Engl J Med 336: 186-195, 1997.

[15] Grotenhermen F. Pharmacology of cannabinoids. Neuroendocrinol Lett 25: 14-23, 2004.

[16] Kong X, Wang X, Xu W, Behera S, Hellermann G, Kumar A,Lockey RF, Mohapatra SS. Natriuretic peptide receptor A as a novel anticancer target. Cancer Res 68: 249-256, 2008.

[17] Campos LA, Cipolla-Neto J, Amaral FG, Michelini LC, Bader M, Baltatu OC. The angiotensin-melatoninaxis. doi: 10.1155/2013/521783, 2013.

[18] Lissoni P, Rovelli F,Messina G,Monzon A,Pensato S,Trampetti R,Porro G, Maestroni G,Merli N, Di Fede G. A review on the neuroendocrine regulation of cytokine secretion: possiblemodulation of the cytokine network by the pineal hormone melatonin and cannabidiol. Oncol Res Rev 2: 1-4, 2019.

[19] Kuklina EM, Glebezdina NS, Nekrasova IV. Role of melatonin in the regulation of differentiation of T cells producing interleukin-17 (Th17). Bull Exp Biol Med 160: 656-658, 2016.

[20] Nagarkatti P, Pandey R, Rieder SA, Hegde VL, Nagarkatti M. Cannabinoidsasnovel anti-inflammatorydrugs. Future Med Chem 1: 1333-1349, 2009.

[21] Platten M, Youssef S, Hur EM, Ho PP, Han MH, Lanz TV, Philips LK, Goldstein MJ, Bhat R, Raine CS, Sobel RA, SteinmanL. Blocking angiotensin-converting enzyme induces potent regulatory T cells and modulates TH1-and TH17-mediated autoimmunity.Proc Natl Acad Sci USA 106: 14948-149534, 2009.

[22] Madhur M, Lob HE, McCann LA, Iwakura Y, Blinder Y, Guzik TJ, Harrison DG. Interleukin 17 promotes angiotensin II-induced hypertension and vascular dysfunctions. Hypertension 55. 500-507, 2010.

[23] Robert M, Miossec P. Effects of interleukin 17 on the cardiovascular system Autoimmun Rev 16: 984-991, 2017.

[24] Lopez-Jaramillo P, Gomez-Arbelaez D, Lopez-Lopez J, Lopez-Lopez C, Martinez-Ortgega J, Gomez-Rodriguez A, Triana-Cubillos S. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. Horm Mol Biol Clin Investig 18: 37-45, 2014.

[25] Lissoni P, Rovelli F, Monzon A, Messina G, Porta E, Porro G, Pensato S, Martin E, Sassola A, Caddeo A, Galli C, Merli N, Valentini A, Di Fede G. COVID-19 disease as an acute angiotensin 1-7 deficiency: a preliminary phase 2 study with angiotensin 1-7 in association with melatonin and cannabidiol in COVID-19-infected subjects. J Infectiology 3: 13-16, 2020.

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